IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Holger G. Gassner et al. Art Unit : 1614
Serial No. : 09/995,022 Examiner : D. Jagoe
Filed : November 26, 2001
Title : METHODS FOR ENHANCING WOUND HEALING

Commissioner for Patents
Washington, DC 20231

RESPONSE

In response to the action mailed January 16, 2002, Applicants respectively request reconsideration and allowance of claims 23 and 32-43 in view of the following remarks.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 23, 32-35, 37-40 and 42 under 35 U.S.C. § 102(b) as being anticipated by Sanders *et al.*, U.S. Patent No. 5,766,605 A. The Examiner asserted that Sanders *et al.* teach "a composition comprising the decongestant neosynephrine® (phenylephrine, a vasoconstrictor), xylocain® spray (lidocaine) and type A botulinum toxin" and that these ingredients were administered to the nasal cavities of anesthetized dogs.

Applicants respectfully disagree. Sanders *et al.* do not disclose a composition containing botulinum toxin with a local anesthetic agent or a local vasoconstrictive agent as recited in claims 23, 32-35, 37-40, and 42, which relate to compositions of botulinum toxin that include either (1) a local anesthetic agent, (2) a local vasoconstrictive agent, or (3) both a local anesthetic agent and a local vasoconstrictive agent. Sanders *et al.* disclose a method for the control of autonomic nerve function that involves administering a therapeutically effective amount of botulinum toxin such that denervation of the neurons is achieved. The method of Sanders *et al.* includes sequentially administering a sedative, a decongestant, a local anesthetic, and then

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botulinum toxin (see column 8, lines 21-31 of Sanders *et al.*). Sanders *et al.* does not disclose a composition containing combinations of botulinum toxin, a local anesthetic, and a local vasoconstrictor. Thus, the Sanders *et al.* patent does not anticipate the claimed compositions, and the Examiner is requested to withdraw the rejection under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 23 and 32-43 under 35 U.S.C. § 103(a) as being unpatentable over Adams *et al.* U.S. Patent No. 4,029,794, in view of Sanders *et al.* U.S. Patent No. 5,766,605 A. The Examiner asserted that Adams *et al.* teach "a toxin such as saxitoxin...along with local anesthetics such as lidocaine," and that "vasoconstrictors may be added for administration..." The Examiner alleged that it was obvious to "substitute the neurotoxin botulinum toxin for the neurotoxin saxitoxin" as they are equivalent and hence a reasonable expectation that "the respective species will behave in a comparable manner or give comparable results in comparable circumstances." The Examiner also asserted that Sanders *et al.* teach "a composition comprising the decongestant neosynephrine® (phenylephrine, a vasoconstrictor), xylocaine® spray (lidocaine) and type A botulinum toxin." The Examiner alleged that it was obvious to substitute the vasoconstrictor epinephrine for the vasoconstrictor phenylephrine as they are equivalent and therefore would be expected to "behave in a comparable manner or give comparable results in comparable circumstances."

Applicants respectfully disagree. Adams *et al.* teaches a local anesthetic composition that includes a mixture of saxitoxin and a conventional local anesthetic compound. Applicants submit that it is not obvious to "substitute the neurotoxin botulinum toxin for the neurotoxin saxitoxin." Saxitoxin and botulinum toxins have different sites and mechanisms of action. Saxitoxin alters the action potential at the voltage-gated sodium channels along the neuron axon and is used for nerve blocks to induce local anesthesia. See, Watters (1995) *Clin Neurol Neurosurg* 97:119-124 (reference AQQ of attached Form 1449). In contrast, botulinum toxins block the release of acetylcholine at the neuromuscular endplate of neurons and are used to induce paralysis. See, specification at page 6, lines 13-14 and Schantz *et al.* (1992) *Microbiol Reviews* 56:86-99 (reference AHH of attached Form 1449).

Saxitoxin and botulinum toxins also have different pharmacokinetic properties. As indicated in the specification, the paralysis induced by saxitoxin does not last as long as the paralysis induced by botulinum toxin, and repeated injections of saxitoxin would be needed. See, for example, the specification at page 7, lines 22-25. Also see Kohane *et al.*, (2000) *Reg Anesth Pain Med* 25(1):52-59 (reference ARR of attached Form 1449), which indicates that the duration of action of saxitoxin is only a few hours. Furthermore, while saxitoxin may be used as a local anesthetic, the effective dose of saxitoxin is relatively close to the lethal dose in animals. See, Schantz *et al.*, *supra*. As indicated in Adams *et al.* and in Schantz *et al.*, *supra*, small amounts of saxitoxin can be mixed with a local anesthetic, which results in a composition that has unusually greater anesthetic effects. The amount of saxitoxin in such compositions (e.g., 1 part saxitoxin per 10,000 parts local anesthetic), however, does not induce paralysis. See, page 92 of Schantz *et al.*, *supra*. Since saxitoxin and botulinum toxins have different sites of action, different mechanisms of action, and different pharmacokinetic properties, the two neurotoxins cannot simply be substituted for one another as there is no reasonable expectation that the two neurotoxins will behave in a comparable manner or give comparable results in comparable circumstances.

The Sanders *et al.* patent does not remedy the deficiencies of the Adams *et al.* patent. As described above, the Sanders *et al.* patent provides a method for the control of autonomic nerve function. The Sanders *et al.* patent does not teach or suggest a composition containing a botulinum toxin, a local anesthetic, and/or a local vasoconstrictor. Therefore, the cited compositions are non-obvious in view of the cited art. Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

CONCLUSION

Applicant asks that claims 23 and 32-43 be allowed. The Examiner is invited to telephone the undersigned agent if it is felt that such would advance prosecution of the application.

A $200 check is enclosed for the two-month extension of time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 6/17/02

Monica McCormick Graham, Ph.D.
Reg. No. 42,600

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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